REMARKS

Claims 1-6 and 15-20 are pending in this application.

Favorable reconsideration is respectfully requested in view of the following remarks.

Typographical changes to Greek letters γ and μ

In the application as filed, these 2 Greek letters appear slightly elevated in the terms, μg, μm and IFN-γ. In the present Amendment, these letters appear relative to other letters as in the previous sentence. This apparently represents a typographical difference in the computer/printer systems used to generate the original application and the present application.

Objection for failure to provide information about provisional application (Page 2 Paragraph 6 (a) of Office Action)

Applicant has amended the specification to include the missing information regarding the provisional application to which domestic priority is claimed.

Objection to drawings (Page 2 Paragraph 6 (b) of Office Action)

With regard to the reference, in the first sentence of the objection, to Figures 1 and 2, the Examiner, in a telephone conversation with the undersigned on November 29, 2001 clarified that there was no objection to Figure 1, but rather to Figures 2, 4-6, and 9-10. Please note that Applicant submits the amended drawings as requested by the Examiner. A second set of amended drawings showing changes circled in

red ink is attached to this Amendment. Also, Applicant has amended the Specification to reflect the panel lettering (A, B, etc.) that appears on the amended Figures. Applicant has amended the specification in that regard on pages 8-10 where the Brief Description of the Drawings occurs. Applicant has not amended the application elsewhere in that regard because he believes that at other places in the specification, reference to the Figure as a whole provides sufficient information to the reader.

Objection to the use of trademark (Paragraph 6 (c) of Office Action)

Applicant has amended the Specification to clarify that Tween 20 is a trademark.

Rejections of Claims 1-4, 6, and 15-18 under 35 U.S.C. 102(b)/103(a) in light of Jackson *et al.* (Paragraph 9 of the Office Action)

The Examiner has rejected Claims 1-4, 6, and 15-18 as being anticipated or obvious over Jackson *et al. (Ann. N. Y. Acad. Sci.* 730: 217-234, 1994).

This rejection is respectfully traversed on the following grounds:

Applicant has carefully considered the Examiner's remarks with regards to Jackson *et al.* It appears to Applicant that Jackson *et al.* does not disclose using encapsulated antigen to elicit a polarized T_H1 response when the vaccine is applied parenterally. Indeed, it appears to Applicant that, in Jackson, when TT-containing microspheres were administered parenterally, a subclass analysis was not performed to differentiate between T_H1- and T_H2-types of immune response. Regarding the rejection under section 103, it does not appear to Applicant that one can extrapolate,

given any data in Jackson, to the conclusion that a polarized T_H1 response could be elicited if encapsulated antigen were to be administered.

Given the large amount of data in Jackson, Applicant respectfully requests the Examiner to point out with line-number specificity to any support for the present rejection should it be maintained.

Rejections of Claims 5 and 19 under 35 U.S.C. 103(a) in light of Jackson *et al.* and Mills *et al.* (Paragraph 10 of the Office Action).

The Examiner has rejected Claims 5 and 19 as being obvious over Jackson *et al. (Ann. N. Y. Acad. Sci.* 730: 217-234, 1994) and further in view of Mills *et al. (Infect. Immun.* 61: 399-410, 1993) as applied to Claims 1 and 15.

This rejection is respectfully traversed on the following grounds:

At least one reason that Claims 5 and 19 are not obvious is because, as noted above, Jackson *et al.* does not make it obvious that the invention of Claims 1 and 15, on which Claims 5 and 19 depend, are obvious.

Applicant reserves the right to present additional reasons as to why Mills *et al.* does not make claims 5 and 19 obvious if necessary.

Rejections of Claims 1-6 and 15-19 under 35 U.S.C. 103(a) in light of Tice *et al.* or Cahill *et al.* (Paragraph 11 of the Office Action).

The Examiner has rejected Claims 1-6 and 15-19 as being obvious over Tice *et al.* (US 6,024,983) or Cahill *et al. (Vaccine* 13: 455-462, 1995).

This rejection is respectfully traversed on the following grounds:

Upon careful review. it appears to Applicant that not only do neither Tice *et al.* nor Cahill *et al.* disclose using an encapsulated antigen in the form of microparticles

to elicit a polarized T_H1-type response when the vaccine is applied parenterally, they do not make such an invention obvious. Tice *et al.* does disclose that the response mediated by microspheres (1-10 micrometer in size) containing an antigen is a humoral immune response. (e.g. column 15, lane 13). Cahill *et al.* does disclose a method of orally or nasally administering an encapsulated antigen in a form of a microparticle, but parenteral (i.p.) administration of FHA was performed with a solution of FHA, not an encapsulated form of FHA. Applicant respectfully submits that such disclosures by Tice *et al.* and Cahill *et al.* are not sufficient basis to extrapolate to Applicant's invention, reflecting the induction of a polarized T_H1 response by parenteral administration of an encapsulated antigen in microparticles of a specified size.

Rejections of Claim 20 under 35 U.S.C. 103(a) in light of Tice *et al.* and Jones *et al.* (Page 6 Section 12 of the Office Action).

The Examiner has rejected Claim 20 as being obvious over Tice *et al.* (US 6,024,983) and in view of Jones *et al. (J. Biotechnol.* 44: 29-36, 1996).

This rejection is respectfully traversed on the following grounds: At least one reason that Claim 20 is not obvious is because, as noted above, Tice *et al.* does not make it obvious that the invention of Claim 15, on which Claim 20 depends, is obvious.

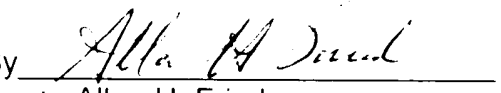
Applicant reserves the right to present additional reasons as to why Jones *et al.* does not make Claim 20 obvious if necessary.

In view of the foregoing remarks, it is respectfully submitted that all of the claims now remaining in this application are allowable and such favorable action is respectfully requested.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

December 20, 2001

By 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please **insert** below the title of the above-identified invention as a first paragraph the following:

-- This application claims the benefit of U.S. Provisional Application No. 60/098,760, filed September 1, 1998.—

Please make the following changes to the Specification:

On page 8, line 18 through page 8, line 25, please **replace** the paragraph with the following paragraph:

-- Figure 2 shows the T_H1/T_H2 responses following parenteral immunization with PTd-PLGA microparticles (batch PTd-1 of Example 2) prepared by solvent evaporation. Three groups of mice received a single dose of 5 μg PTd-PLGA, PTd with alum or in solution in PBS. The levels of IFN-γ (see Fig. 2A) and IL-5 (see Fig. 2B) were determined by specific immunoassays in cultured spleen cells three days after stimulation with PT. Medium = negative control; iPT = inactivated PT; B pertussis = active pertussis bacteria and anti-CD/PMA = the positive control anti-CD3 antibody/phorbol 12-myristate-13 acetate;--

On page 9, line 4 through page 9, line 2, please **replace** the **three paragraphs** with the following three paragraphs:

-- Figure 4 shows the serum antibody titres to PTd following i.p. administration as described in Example 7 of PTd +FHA in PLGA (see Fig. 4A) (5μg each of PTd and FHA entrapped in PLGA microparticles according to Example 2 and 3); PTd + FHA +

alum (see Fig. 4B) (5μg each of Ptd and FHA adsorbed onto alum; and PLGA (see Fig. 4C) (i.p.) (empty PLGA microparticles) to balb/c mice;

Figure 5 compares the T_H1/T_H2 responses following parenteral immunization of balb/c mice with PTd + FHA in PLGA (5μg each of PTd and FHA entrapped in PLGA microparticles according to Example 2 and 3; 4 animals) and PTd + FHA + alum (5μg each of PTd and FHA adsorbed onto alum; 4 animals). The levels of IFN-γ (see Figs. 5A and 5B) and IL-5 (see Figs. 5C and 5D) were determined by specific immunoassays in cultured spleen cells three days after stimulation with PT. iPt = inactivated PT; FHA = filamentous haemagglutinin; B pertussis = active pertussis bacteria and anti-CD3/PMA = the positive control anti-CD3 antibody/phorbol 12-myristate-13 acetate;

Figure 6 shows the T_H1/T_H2 responses following i.p. administration of low dose (1 μg) FHA encapsulated in PLGA wherein Fig. 6A reflects the levels of γ-IFN, and Fig. 6B reflects the levels of IL-5. Spleen cells from individual mice were stimulated with medium alone (0), inactivated PT (PT), filamentous haemagglutinin (FHA), active pertussis bacteria (BP) and the positive control anti-CD3 antibody/phorbol 12-myristate-13 acetate (PMA/CD3); --

On page 10, line 8 through page 10, line 20, please, **replace** the two paragraphs with the following two paragraphs:

-- Figure 9 shows the T_H1 response (IFN-γ) and the T_H2 response (IL-5) following i.m. immunization with Treatment F of Example 10. The levels of IFN-γ (see Fig. 9A) and IL-5 (see Fig. 9B) were determined by specific immunoassays in

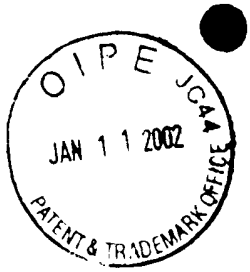
cultured spleen cells from 5 animals (Mouse 1 through Mouse 5) three days after stimulation with PT. BG = negative control; PT-inactivated PT; B. pert = active pertussis bacteria and PMA/aCD3 = the positive control anti-CD3 antibody/phorbol 12-myristate-13 acetate; and

Figure 10 shows the T_H1/T_H2 responses following parenteral immunization with coacervated nanoparticulate Treatments A-F of Example 11. The levels of IFN-γ (see Fig. 10A) and IL-5 (see Fig. 10B) were determined by specific immunoassays in cultured spleen cells three days after stimulation with PT. iPT-1 = activated PT (1.0 μg /ml); iPT-5 = inactivated PT (5.0μg/ml); FHA-1 = FHA (1.0μg /ml); FHA-5 = FHA (5.0 μg /ml); BP = active pertussis bacteria and PMA/CD3 = the positive control anti-CD3 antibody/phorbol 12-myristate-13 acetate. –

On page 13, line 24 through page 14, line7, please **replace** the paragraph with the following paragraph:

-- The morphology and the particle size of the KLH-PLGA particles were examined by scanning electron microscopy (SEM) using a Leica Cambridge S360. Samples were mounted on stubs, gold coated and scanned at magnifications of x3,000 – 10,000. Particle size assessment by SEM was carried out by dividing the micrographs at the 5,000 or 10,000 magnification into different fields and counting the number of particles greater and less than 3 microns and 5 microns. Particle size determination was also carried out by laser diffractometry using a Malvern Mastersizer S Ver. 2.14. The microparticles were suspended in filtered 0.1% [Tween] TWEEN 20, sonicated for 5 minutes and analyzed with continuous stirring. KLH-

PLGA particles prepared as detailed above were found to have a smooth spherical appearance and a D50% of 2.5 μm by laser light diffraction. By SEM, it could be seen that at least 50% of the particles had a diameter less than 5 microns.--



CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT including amended figures, PETITION FOR EXTENSION OF TIME and TRANSMITTAL FORM re Application Serial No. 09/386,266 are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this 20th day of December, 2001.

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